DERMOVASCULAR ACTION OF ESTROGEN, THE OVARIAN FOLLICULAR HORMONE*

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In the treatment of neurovascular disturbances of the climacteric, one of the most used therapeutic agents is estrogen, the ovarian follicular hormone. Its effectiveness in the majority of cases is now well established. Little is known, however, concerning the mechanism by which relief from hot flushes is afforded. It is known that subsidence of symptoms coincides with the disappearance of a gonadotropic substance (arising in the pituitary?) in the urine, but the hypothesis that relief from the vascular disturbance of the menopause is the result of suppression of pituitary-overactivity leaves unanswered the question of how suppression of the heightened vasomotor irritability takes place.

The experiments described below were made, therefore, to ascertain what demonstrable peripheral vascular effects, if any, estrogen has. Observations have been made in the ear of the rabbit, and on the human finger both in men and in women in, or near, the menopause. The results of the experiments on the ear of the rabbit have been published in detail elsewhere, (Reynolds and Foster, 1940) so these will be briefly summarized here, along with data obtained in the human male (cf. Reynolds and Foster, 1939). Study of the dermovascular action of estrogen in menopausal women is still in progress, so the following account of these experiments should be considered as a preliminary report.

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I. DERMOVASCULAR ACTION OF ESTROGEN IN THE EAR OF THE RABBIT[1]

In this work, the effect of estrogenic hormone on the blood vessels of the skin was observed in the transilluminated ear of the rabbit. Ovariectomized animals were used in order to eliminate a source of estrogen in the organism. At the time of an experiment, the rabbit was given a hypnotic dose of a barbiturate anesthesia (Dial, Ciba), and then so placed that it was lying comfortably on a padded board, protected from drafts. In order to be certain that the condition of the blood vessels was not modified primarily by changes in temperature, records were kept of the rectal temperature, ear temperature (by means of a sensitive thermocouple) and of room temperature.

As a result of a number of preliminary experiments, we were able to confirm the extensive observations of Grant (1935–36) on the ear of the rabbit, both as to the types of blood vessels found in these tissues and the effect of changes in temperature upon them. This investigator determined that there are three principal types of blood vessels to be seen: A) the main vessels (meaning the central artery, its main branches, and chief veins); B) the small vessels (meaning the network of small arteries and veins that cover the blade of the ear and are visible to the naked eye); C) the minute vessels (including the arterioles, venules, arteriovenous-anastomosis and the capillaries which are indistinguishable to the naked eye but give rise to the ground color of the ear). The state of the minute vessels is readily gauged by this ground color. There are two especially significant facts concerning the last, or C group of vessels above. First, it was observed by Grant that denervation of the ear does not affect their responses to chemical, mechanical, or thermal stimuli, and second, the C group of vessels resemble qualitatively the blood vessels of the human skin to such stimuli. The blood vessels of the rabbit ear, however, are more liable to changes in temperature than are those of human skin, apparently because

[1] Supported by grants from the Committee on Research in Endocrinology, National Research Council, the Committee on Scientific Research, A. M. A., and the Josiah Macy, Jr. Foundation.

the ears of the rabbit constitute a primary route for heat-loss, while in the human, heat-loss takes place from a relatively much larger surface.

The effect of estrogen, it was repeatedly observed, is limited to the smallest vessels lying beyond the arterioles, namely, the

FIG. 1. Diagram of blood vessels in a field of the ear of an ovariectomized rabbit. *A*, before injection of estradiol; *B*, fourteen minutes later. (Reprinted from the Jour. Pharmacol. Exp. Therap., **68:** 179, 1940.)

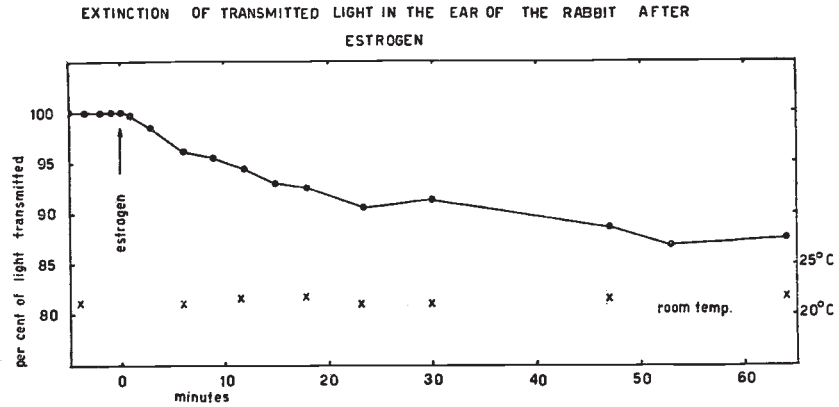

FIG. 2. Curve of light-extinction of transmitted light in the ear of a rabbit before and following injection of estrogen. The intensity of transmitted light is diminished as vasodilatation takes place. A Lange photoelectric cell was employed.

capillaries and venules and possibly the arteriovenous anastomoses. It is characterized by dilatation of the vessels within the first three to twenty minutes. This is seen by opening of an extensive network of vessels which may be detected in only fragmentary bits during the preinjection period. In addition

numerous capillary loops open, also. Red blood cells frequently may be seen trailing by. The dilatation persists throughout the period of observation, as shown in figures 1 and 2.

Several considerations show that only the smallest vessels in the ear are affected. First, those which respond are demonstrable in the C group, as noted above; second, the measurements of skin temperature show that at moderate or low room temperatures (ca. 18°C. to 24°C.), the vasodilatation takes place either with no change in ear temperature or with a fall in skin temperature (see fig. 3). Third, the ground color of the ear

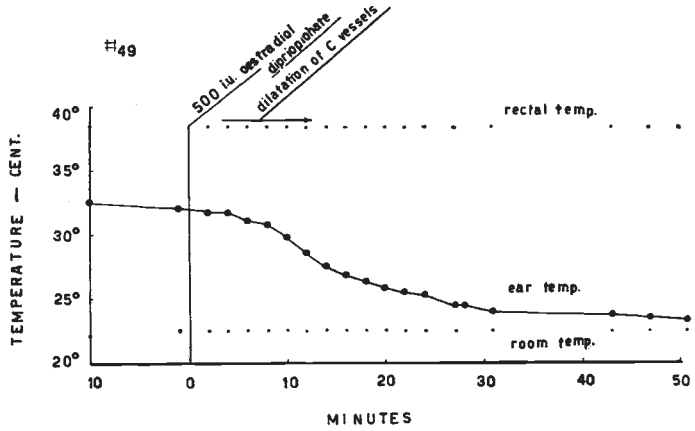

FIG. 3. Curves of skin temperature, rectal temperature and room temperature in an ovariectomized rabbit before and following injection of estrogen. The decrease in skin temperature occurred as a result of decreased blood flow in the ear when the smallest blood vessels dilated under the influence of estrogen.

becomes pinkish—an evidence of moderate dilatation of the smallest capillaries and venules, as Grant has established.

Such experiments performed under suitable conditions show, therefore, that while estrogen causes dilatation of the minute vessels (capillaries and venules), the rate of blood flow through the ear does not increase materially. This varies, rather, with the requirements for heat-loss which vasodilatation of the smallest vessels imposes in the regulation of normal body temperature under different experimental conditions. Nevertheless, it is clear on physiological grounds that with an enlarged capillary

bed in the ears, the possibility for increased heat-loss, with less arteriolar (vasomotor) adjustment is readily possible.

II. DERMOVASCULAR ACTION OF ESTROGEN IN THE HUMAN

In the male.[1] In twenty-nine experiments on twenty males, increase in finger-volume was demonstrated with a plethysmograph nineteen times in twelve of the subjects. Six failed to respond to the hormone for unknown reasons, and two responded to the injection of corn oil alone as well as to the hormone. The ast two are not included in the group of subjects considered to

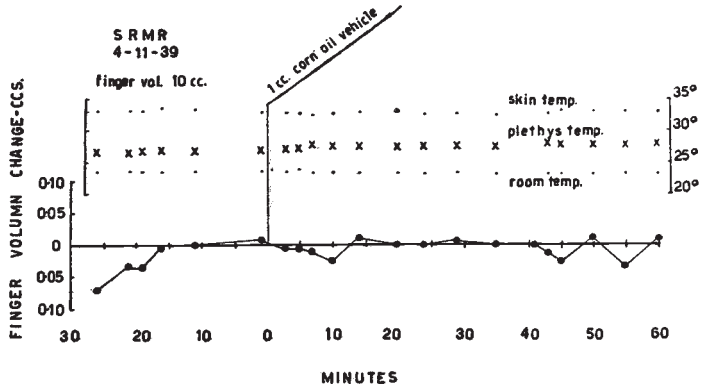

FIG. 4. Non-effect of corn oil on finger volume (in the human male, recorded plethysmographically). (Reprinted from the Jour. Clin. Invest., **18:** 651, 1939.)

be specifically susceptible to the dermovascular action of estrogen. In the hormone-responsive group, none responded to corn oil (see fig. 4), although all injections, hormone and corn oil, were made as "unknowns" to the subjects. The hormone (usually 10,000 rat units) was injected intramuscularly into the free arm of the subject who was comfortably seated.

A typical response is shown in figure 5. Within three to fifteen minutes, the volume of the finger begins to increase, occasionally after a transient decrease (i.e. vasoconstriction resulting from nervousness at the time of injection). The finger-volume becomes steadily larger for at least half an hour, although more often the period of change lasts forty-five minutes to an

hour. The finger remains large for a period in excess of the maximum time of observation (two hours). During the period of vasodilatation, there is no perceptible rise in nail bed temperature, or in the temperature of the plethysmograph. This means, therefore, that the volume-change is effected without a significant alteration in the rate of blood flow. It therefore follows that vasodilatation occurs beyond the smallest arterioles.

The magnitude of the change in finger-volume, may be mentioned in passing. The smallest percentage change observed

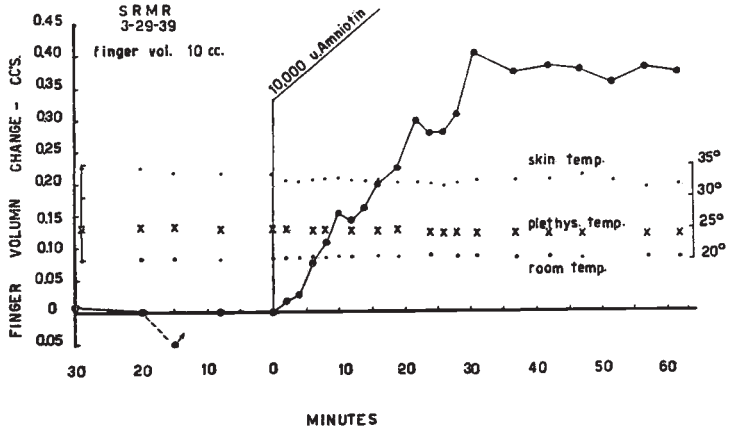

FIG. 5. Effect of estrogen, administered intramuscularly, on finger volume in the human male. (Reprinted from same article as fig. 4.)

was 0.8%, the largest 8.3%, and the mean, 4.6%. In order to appreciate the extent of this volume-change, it should be pointed out that the fleshy part of four embalmed fingers was 56%. Since the above noted increase in finger-volume was limited to such parts of the finger, the actual volume-change was about double the values just quoted.

In women in menopause.[2] In this work, twenty-five women have been studied. Twelve were in surgical menopause, thirteen in natural menopause. All were carefully selected from a large

[2] Supported by grants from the Committee on Research in Endocrinology, National Research Council, and the Josiah Macy, Jr. Foundation.

group of women attending the outpatient clinic at the Greenpoint City Hospital.[3] The necessary condition for selection in this work was that the patient had to have as a primary complaint frequent and intense hot flushes of menopausal origin of sufficient severity that she sought medical relief. In addition, an attempt was made to select patients who showed no other important clinical findings. Even so, some presented various kinds of nervous instability (e.g., involutional melancholia, paranoid dementia precox, and nervous tension resulting most often from poor family conditions). As the work developed, several had other disabilities which rendered them unsuitable for continued observation. These included cases of hypertension, rheumatism, proliferative hypertrophic arthritis, malnutrition and endocrine obesity. The patients attended the clinic for varying periods of time—some (eight) for several weeks or a month until it was evident that some other type of treatment was indicated, and others (seventeen) are continuing for periods now ranging from three to seven months. Two of these are sufficiently relieved that they now come in at long and irregular intervals. All the cases studied, however, have yielded some useful information especially with regard to the role of psychic factors involved in the menopausal flush. In this report, emphasis will be laid on the more objective vascular data that have been obtained.

Character of the response. Two types of dermovascular response have been observed in these patients. One, like that seen in the male, consists of a slow rise in the curve to a sustained plateau (see fig. 6). The amplitude of this response varies with conditions that are not fully known at the present time. One appears to be the length of time the patient has been under treatment, another, the mental state of the subject. Careful review of the data now obtained show it not to be associated

[3] This work is made possible through permission granted by Dr. Thurston Scott Welton, Chief of Service in the clinic in which we are working. Associated with the writer in this is Dr. Sanford Kaminester, of the Department of Obstetrics and Gynecology, Long Island College of Medicine, Dr. Stewart Schloss, and Miss Frances I. Foster.

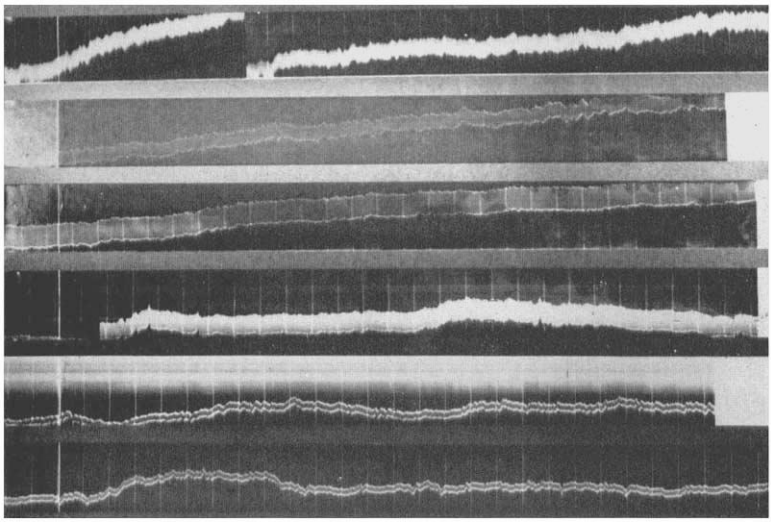

FIG. 6. Curves of the effect of estrogen on finger volume in an ovariectomized woman. Top, effect of estradiol dipropionate on March 6th; 2nd line, effect on March 13th; 3rd line, on March 23rd; 4th line, April 17th; 5th line, May 1st; bottom line, on May 29th. See figure 8 for the graph summarizing this case. The vertical white line in each curve indicates the conclusion of the injection of estrogen. The sudden drop in the curve in the top line indicates the point where the droplet was moved to the starting point for recording the rest of the response. In the 4th line, the droplet was raised to the recording level. The first three curves are the "plateau type" of dermovascular response, the last three, the "flush type" (see text). It will be noted that there was mild exacerbation of flushes on the last three curves attributable to uncertain conditions at home, or to worry over uterine bleeding which was induced after the estrogen level was decreased (see fig. 8). Time, minutes.

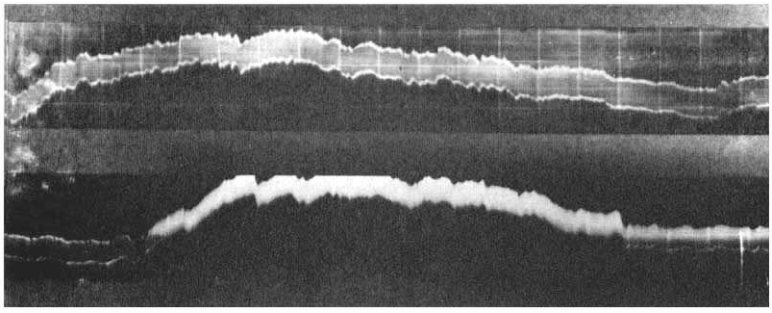

FIG. 7. Plethysmographic records of true menopausal flushes, uncomplicated by injection of estrogen. Appreciable vasodilatation occurred. For temperature changes, see figure 10.

with the type of estrogen used,[4] and not with seasonal variations. Data have been obtained from November throughout the winter months and into June, but the trend of the dermovascular responses is roughly characteristic for each person, whether treatment was commenced in the winter or in the spring.

The second type of response to estrogen is seen less frequently. It is characterized by a slow increase in finger-volume to a maxi-

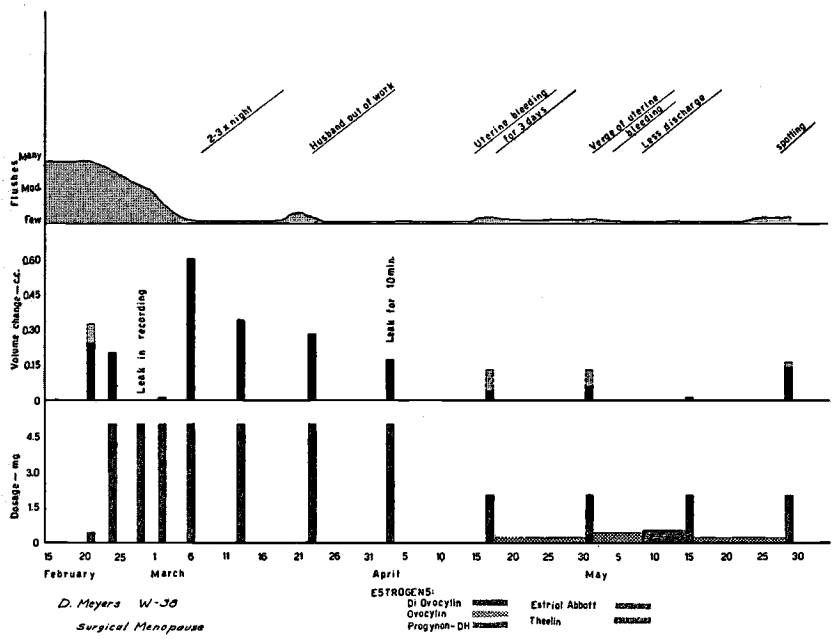

FIG. 8. Summary of the dermovascular responses in one patient who experienced satisfactory relief from menopausal flushes, but still requires treatment See figure 6.

mum, followed by partial subsidence to a plateau which is maintained for the period of observation. Such a response is shown in the bottom curve of figure 6, and it is not unlike the response

[4] The estrogens used have been liberally supplied by commercial concerns as follows: estrone, Estrone Abbott, and Theelin, Parke, Davis & Co.: estradiol for oral use, Progynon D-H Schering Corp., Ovocylin, Ciba; estriol, Estriol Abbott; estradiol benzoate, Progynon-B, Schering Corp.; estradiol dipropionate, Di-Ovocylin, Ciba.

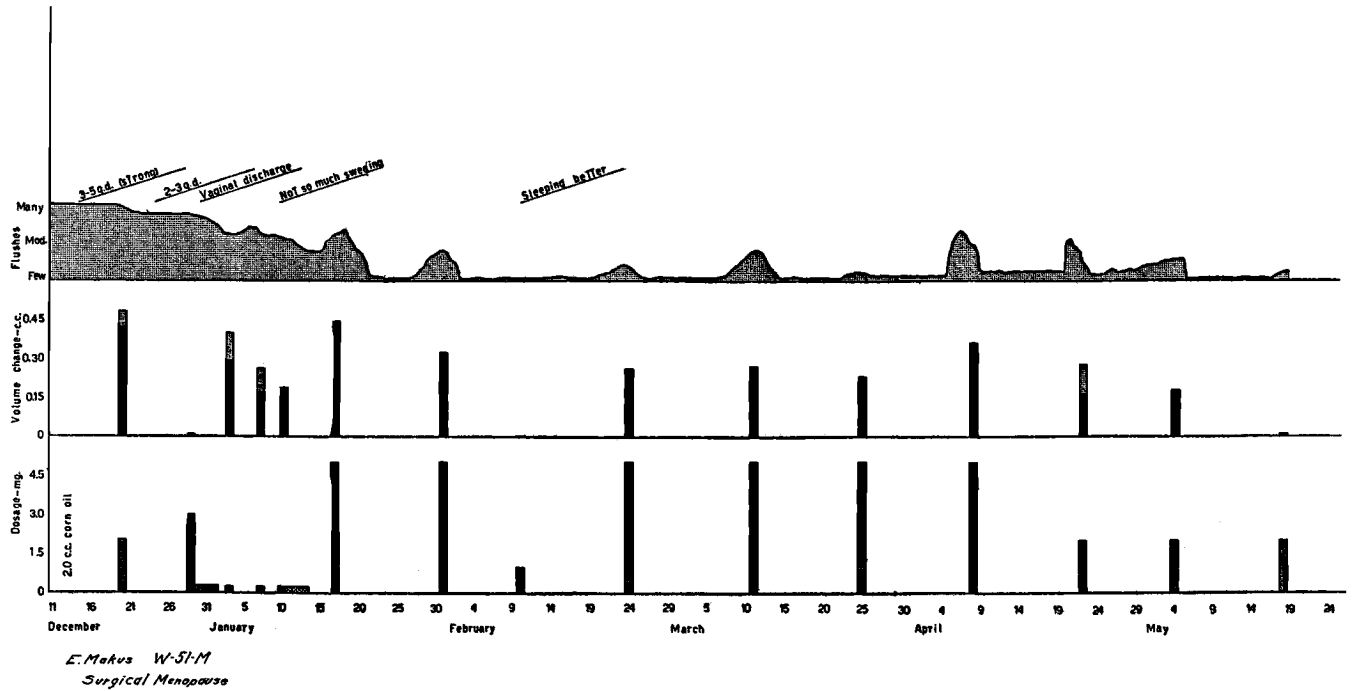

FIG. 9. Summary of dermovascular responses in a patient whose flushes return with moderate severity prior to returning to the clinic.

of a true menopausal flush, two examples of which are shown in figure 7. In the graphs (figs. 8 and 9), the occurrence of the flush-type of response is indicated by the stippled areas above the black bars in the row marked "volume-change." With the exception of one of the subjects in whom this type of response usually occurs, the flush-type of response has been observed either very early in the course of treatment when the subject was in a highly nervous state, or at later times, when some exciting or disturbing factors are present. When it occurs, the patient experiences uncomfortable sensations; she feels warm over the neck, back, face and arms; she perspires and appears flushed. With continued estrogen therapy, the plateau-type of dermovascular response is usual.

Estrogen dosage and the dermovascular response. At the outset of this work, three patients were transferred from the endocrine clinic in the hospital where they had been receiving intensive estrogen treatment. To our surprise, these patients never exhibited a pronounced dermovascular response, while those who were just commencing treatment showed considerable responsiveness to the hormone. It was apparent from the first, therefore, that the amplitude of the response is not governed by the amount of hormone injected, but rather by the condition of the subject at the time of the injection.

The dosage of the several estrogens employed may not be compared with each other, since there is not yet agreement on the relative physiological potencies of these substances. With each type of estrogen, however, responses have been obtained to two or more levels of dosage. When all the cases were reviewed with this in mind, we failed to find correlation between dose and response, even in the same subject. If, however, comparison is made of the effects of two or three dosages on patients who are *free of menopausal flushes*, there are some instances which suggest that the amplitude of the finger-volume change is affected by the dose. This is shown in figures 8 and 9, where one or two milligrams appear to give smaller responses than five milligrams of estradiol-dipropionate. In another case, however, there is clearly no demonstrable relationship between dose and

effect, despite the fact that the subjective symptoms of the menopause were well under control.

Duration of treatment and the response. There is no simple statement to describe the effect which prolonged estrogen therapy will invariably have on the dermovascular responses. Several women have yielded small responses at the outset, while most have given large reactions first. These tend to become progressively smaller as treatment continues. A few women have given variable responses throughout most of the course of treatment. It is evident from examination of all the records, however, that the size of the response is in general proportional to the severity and frequency of the flushes. As examples of this, one sees in figure 9 that the incidence of flushes is usually accompanied by larger responses than those seen in figure 8, in which case there was persistent relief from the flushes, and the finger-volume changes were for the most part small.

Relation of menopausal flush to the dermovascular reaction. In conclusion, comparison may be made of the chief characteristics of the dermovascular reaction to estrogen and the skin changes which occur during a menopausal flush. Several such menopausal flushes, uncomplicated by the injection of estrogen, have been observed from time to time. Some were obtained while the subject was seated for the plethysmographic recording, and a few were obtained while records of vaginal, face and leg temperatures were being recorded.

The menopausal flush differs from the plateau-type of response described above in two respects: it attains a maximum very quickly (see fig. 7), it usually subsides rather quickly, and it is usually of ten to fifteen minutes' duration. This last feature is interesting, since the patient notices,—and minds,—the flush most in the early, rising phase. In contrast to this, the plateau-type of dermovascular response is rarely associated with an unpleasant sensation of warmth in women. This was also found to be so in the earlier study on men.

There is a further difference between the dermovascular response of the plateau-type and the menopausal flush. In the former, there is no measureable increase in skin temperature,

as noted in the earlier study (Reynolds and Foster, 1939). In the flush, there is an appreciable increase in skin temperature, as shown in figure 10 where temperature measurements during such a response are recorded. Although the flush in this case, and in others observed in the same patient, was associated with a rise in internal (vaginal) temperature, this was not found to be the case in two other patients. The relationship of surface to internal temperatures must await more extended studies.

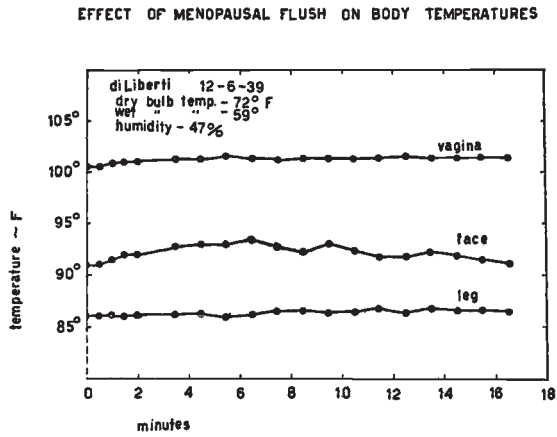

FIG. 10. Summary of temperature data of vaginal, face and leg temperatures on a woman in natural menopause who experienced a flush at the time of observation. Note the increase in skin temperature, but the lack of it in the dermovascular response shown in figure 5. See text for the basis of this difference between the flush and the dermovascular effect of estrogen.

The significance of the difference in temperature characteristics of the two vascular responses may be mentioned in closing. The fact that vasodilatation of the finger takes place without a concomitant rise of skin temperature suggests that the change involves the blood vessels lying beyond the arterioles, and that there is little or no change in the rate of blood flow through the finger. In the menopausal flush, however, where there is both dilatation and an increase in skin temperature, there is an appreciable increase in the rate of blood flow through the skin, clearly as the result of arteriolar dilatation in the affected areas. There is in the menopausal flush, accordingly, intermediation

of nervous factors to bring about a diminution of arteriolar tone, as there clearly is in the sweating which accompanies this response, also (cf. Reynolds, 1939). The dermovascular response to estrogen, on the contrary, involves vessels which are not modified by nervous activity, and it would appear that the consequences of estrogen therapy in the menopause include an alteration in the condition of the smallest vessels of the skin. This is attested by the development of a "tolerance" to estrogen as relief is afforded, so far as the dermovascular effects are concerned. Further experiments on the quantitative aspects of the tache reactions of the skin will have to establish this new functional state of the minute vessels. Moreover, further experiments will be necessary to demonstrate the extent to which estrogen may be effective in relieving menopausal flushes through alteration in the relation of the skin and internal temperatures by virtue of the dermovascular action which estrogen clearly has.

SUMMARY

1. A review is given of the experiments reported in earlier papers on the vasodilating effect of estrogen on the capillaries and venules in the skin of the ear of the rabbit and in the human male. The increase in finger-volume involves the capillaries and venules, and does not alter appreciably the rate of blood flow through the skin. The response is in the same direction, though less than that seen in the genital tract following injection of estrogen.

2. A summary is made of work now in progress on the dermovascular effect of estrogen in women in menopause. It is shown that two types of response may occur, one, a sustained plateau, the other, a flush-type of response. The latter is observed in women who are nervous before treatment, or during a period of return of symptoms in the course of treatment. The dermovascular effect of estrogen appears to become less marked as relief from vasomotor disturbances taken place.

3. Comparison is made of the menopausal flush and the dermovascular reaction to estrogen. It is shown that in both vasodilatation occurs, but that in the menopausal flush the effect is

in part due to arteriolar dilatation, and in the estrogen-response, the smallest vessels beyond the arterioles are concerned. The former involves intermediation of nervous activity (inhibition of arteriolar tone), the latter, appears to be a direct effect of the hormone on tissues in or about the blood vessels.

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DISCUSSION

DR. JAMES B. HAMILTON, *New Haven:* I wish to compliment Dr. Reynolds on the work he has been doing. We have been studying by use of the spectrophotometer, the effect of sex hormones on pigments in the skin of castrate men—work done in conjunction with Dr. Edward Edwards of the Harvard Medical School and Dr. S. Q. Duntley of Massachusets Institute of Technology. Following administration of hormone substance we have seen responses somewhat similar in type to those found by Dr. Reynolds. So that what he has described applies also in the male and to some extent, unpredictable at present, is simulated by male hormone substances.

DR. HERMAN SHARLIT, *New York City:* This presentation, it would appear to me, has a very direct application to dermatologists, particularly with respect to public health measures.

We are all aware that the estrogenic hormone is absorbed through the skin, and that cosmetic manufacturers, for quite a few years now, have been putting estrogenic hormones in creams.

The attitude of the medical profession with respect to this procedure has been to decide whether this was safe from the point of view of the larger problem of carcinogenesis. From this type of experimentation, it would appear definitely that estrogen could very well form a basic drug in the pharmacological sense, since it would influence the capillary size of the skin. In this respect, such a product, while in itself not very important, would be of some value in determining to what extent it would be permissible to introduce its distribution as a cosmetic. Time alone will tell what such a cosmetic can do, and how safely it may be used.

DR. THEODORE CORNBLEET, *Chicago:* I am interested in the relationship between estrogen and the behavior of the blood vessels of the skin under its influence. They can readily be studied in Rosacea. Rosacea appears usually during the age period when the follicular hormone may be expected to wane.

Oily extracts of ovary, such as the product Sistomensin (Ciba) contract telangiectases and blanch the suffused areas of rosacea in many cases. The synthetic estrogens are useful for this purpose, but I think not as rapidly as the extract of

whole ovary. The most rapid and complete results occurred in women towards and beyond the menopause. Younger women did not respond favorably. A few men improved partially after prolonged therapy. The degree of their changes lay between that in the menopausal and the young women. In a forthcoming publication I shall discuss measures other than the administration of estrogen, which are more effective in men. Just how permanent these results will be I cannot, as yet, say, although I have been following some of these patients for several years. In spite of that, I am still rather conservative in my judgment. In several cases, it seems apparent that the improvement is permanent. I think that estrogen unquestionably has a potent action on the blood vessels of the skin and influences, among other things, their caliber. These oily extracts of ovary or estrogens do not influence the papules or popular pustules in patients with *Acne rosacea*. They act only on the *blood vessel* dilatations.

DR. SAMUEL R. M. REYNOLDS, *Brooklyn, N. Y.:* We have used Perandren (male sex hormone) in some women and have obtained the same type of results as Doctor Hamilton. I did not have time to go into the literature, and do not profess to be familiar with the literature on the relationship between the sex hormones and the clinical applications as far as dermatology is concerned.

Dr. Sprunt of Duke University has carried out observations showing the absorbability of various types of matter injected into the skin, as affected by the hormonal state of the animal, with particular regard to the sex hormones.

I did not go into the mechanism of the vaso-dilatation resulting from injection of estrogen. In the rabbit this vaso-dilatation can be inhibited by the previous injection of atropin.

It would appear on this basis that the vaso-dilatation is associated with an increase in the amount of acetylcholine present in the tissues. In order to test this, we have made determinations on the acetylcholine concentration in various tissues. We have not been able to find measurable amounts of acetylcholine in the skin of the rabbit, the cat or the rat, but we could obtain measurable quantities after the injection, in the nasal mucosa.

We have also shown that this same type of response is associated with the hyperemia which is found in uterine tissues. We can recover very appreciable quantities of acetylcholine after the injection.

In closing, I should like to say a word about carcinogenesis. I am not impressed with this as a danger in the long use of estrogenic substances in the treatment of menopause. Only one aspect of a patient's history would make me question the likelihood of such a danger, and that is whether any of the patient's relatives have had carcinoma. I know no human case in the literature in which carcinoma has been induced specifically by any of the sex hormones. One can induce carcinogenesis only by the injection over a relatively long period of time, in high dosage, in animals already highly susceptible to cancer. This has been observed only in mice and rats.